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Metalloprotease activity in skeletal muscle cells is potentiated by paracrine factors released by mesenchymal stromal cells

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Injured skeletal muscle can undergo repair spontaneously *via* satellite cells activation. However, increasing evidence suggest that the mere presence of these cells is not sufficient to ensure a rapid functional regeneration of the injured muscle, and that the release of appropriate factors and the establishment of suitable microenvironment are even more important in determining the effectiveness of the myogenic response. In particular, extracellular matrix remodelling is essential for myoblast migration, differentiation and fusion at the sites of muscle injury. On these basis, in the present study we evaluated the ability of C2C12 myoblasts and satellite cells to express and release metalloproteases in the course of differentiation and whether this activity could be regulated by factors released by MSCs. This with the aim of expanding our knowledge on the paracrine effects of MSCs on skeletal muscle repair/regeneration. The results showed that the administration of conditioned medium from MSCs (MSC-CM) up-regulated the expression and promoted MMP-2 and MMP-9 activation in the cultured myoblasts, as judged by Western blotting, confocal immunofluorescence and gelatinase/collagenase assay. Similar results were obtained when MSCs were separated from the myoblasts by polycarbonate membranes, enabling diffusion of soluble factors while preventing the physical contact between the two cell types. Interestingly, in the single fiber experiments, it was possible to reveal that MSC-CM administration promoted satellite cell mobilization and fusion into multinucleated myotubes. These findings add new information on the effects of MSC on the skeletal muscle healing, and suggest that growth factors and cytokines released by these cells may play a pivotal role not only in the modulation of tissue fibrosis but also in the differentiation of satellite cells.

Keywords: Skeletal myoblasts, mesenchymal stromal cells, metalloproteinases, matrix remodelling.